

CLAIMS

1. DNA coding for a TNF receptor protein or a fragment thereof, wherein said DNA coding said TNF receptor protein has the formula

10 ATG GGC CTC TCC ACG GTG CCT GAC CTG CTG CTG CCA CTG GTG
CTC CTG GAG CTG TTG GTG GGA ATA TAC CCC TCA GGG GTT ATT
GGA CTG GTC CCT CAC CTA GGG GAC AGG GAG AAG AGA GAT AGT
GTG TGT CCC CAA GGA AAA TAT ATC CAC CCT CAA AAT AAT TCG
ATT TGC TGT ACC AAG TGC CAC AAA GGA ACC TAC TTG TAC AAT
GAC TGT CCA GGC CCG GGG CAG GAT ACG GAC TGC AGG GAG TGT
GAG AGC GGC TCC TTC ACC GCT TCA GAA AAC CAC CTC AGA CAC
TGC CTC AGC TGC TCC AAA TGC CGA AAG GAA ATG GGT CAG GTG
GAG ATC TCT TCT TGC ACA GTG GAC CGG GAC ACC GTG TGT GGC
TGC AGG AAG AAC CAG TAC CGG CAT TAT TGG AGT GAA AAC CTT
TTC CAG TGC TTC AAT TGC AGC CTC TGC CTC AAT GGG ACC GTG
CAC CTC TCC TGC CAG GAG AAA CAG AAC ACC GTG TGC ACC TGC
20 CAT GCA GGT TTC TTT CTA AGA GAA AAC GAG TGT GTC TCC TGT
AGT AAC TGT AAG AAA AGC CTG XAG TGC ACG AAG TTG TGC CTA
CCC CAG ATT GAG AAT GTT AAG GGC ACT GAG GAC TCA GGC ACC
ACA GTG CTG TTG CCC CTG GTC ATT TTC TTT GGT CTT TGC CTT
TTA TCC CTC CTC TTC ATT GGT TTA ATG TAT CGC TAC CAA CGG
TGG AAG TCC AAG CTC TAC TCC ATT GTT TGT GGG AAA TCG ACA
CCT GAA AAA GAG GGG GAG CTT GAA GGA ACT ACT ACT AAG CCC
CTG GCC CCA AAC CCA AGC TTC AGT CCC ACT CCA GGC TTC ACC
CCC ACC CTG GGC TTC AGT CCC GTG CCC AGT TCC ACC TTC ACC
TCC AGC TCC ACC TAT ACC CCC GGT GAC TGT CCC AAC TTT GCG
GCT CCC CGC AGA GAG GTG GCA CCA CCC TAT CAG GGG GCT GAC
30 CCC ATC CTT GCG ACA GCC CTC GCC TCC GAC CCC ATC CCC AAC
CCC CTT CAG AAG TGG GAG GAC AGC GCC CAC AAG CCA CAG AGC
CTA GAC ACT GAT GAC CCC GCG ACG CTG TAC GCC GTG GTG GAG
AAC GTG CCC CCG TTG CGC TGG AAG GAA TTC GTG CGG CGC CTA
GGG CTG AGC GAC CAC GAG ATC GAT CGG CTG GAG CTG CAG AAC
GGG CGC TGC CTG CGC GAG GCG CAA TAC AGC ATG CTG GCG ACC
TGG AGG CGG CGC ACG CCG CGG CGC GAG GCG AGC CTG GAG CTG
CTG GGA CGC GTG CTC CGC GAC ATG GAC CTG CTG GGC TGC CTG
40 GAG GAC ATC GAG GAG GCG CTT TGC GGC CCC GCC GCC CTC CCG
CCC GCG CCC AGT CTT CTC AGA TGA

40 or a fragment or a degenerate variant thereof.

45 2. DNA coding for a secretable TNF-binding protein,
having the formula

5 R² GAT AGT GTG TGT CCC CAA GGA AAA TAT ATC CAC CCT CAA
AAT AAT TCG ATT TGC TGT ACC AAG TGC CAC AAA GGA ACC TAC
TTG TAC AAT GAC TGT CCA GGC CCG GGG CAG GAT ACG GAC TGC
AGG GAG TGT GAG AGC GGC TCC TTC ACC GCT TCA GAA AAC CAC
CTC AGA CAC TGC CTC AGC TGC TCC AAA TGC CGA AAG GAA ATG
GGT CAG GTG GAG ATC TCT TCT TGC ACA GTG GAC CGG GAC ACC
GTG TGT GGC TGC AGG AAG AAC CAG TAC CGG CAT TAT TGG AGT
GAA AAC CTT TTC CAG TGC TTC AAT TGC AGC CTC TGC CTC AAT
GGG ACC GTG CAC CTC TCC TGC CAG GAG AAA CAG AAC ACC GTG
TGC ACC TGC CAT GCA GGT TTC TTT CTA AGA GAA AAC GAG TGT
GTC TCC TGT AGT AAC TGT AAG AAA AGC CTG GAG TGC ACG AAG
TTG TGC CTA CCC CAG ATT GAG AAT

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wherein R² is optionally absent or represents DNA coding for a polypeptide which can be cleaved in vivo; or a degenerate variant thereof.

20 3. DNA according to claim 2, coding for secretable TNF binding protein, wherein R² represents DNA which codes entirely or partly for a signal sequence.

25 4. DNA according to claim 2, characterized in that R² has the formula CTG GTC CCT CAC CTA GGG GAC AGG GAG AAG AGA.

30 5. DNA according to claim 3, characterized in that R² represents R³ CTG GTC CCT CAC CTA GGG GAC AGG GAG AAG AGA, wherein R³ represents DNA coding for a signal peptide.

35 6. DNA according to claim 5, characterized in that R³ represents

ATG GGC CTC TCC ACC GTG CCT GAC CTG CTG CCA CTG GTG
CTC CTG GAG CTG TTG GTG GGA ATA TAC CCC TCA GGG GTT ATT
GGA

40 7. A nucleic acid which hybridizes with the DNA defined in claim 1 or 2 under conditions of low stringency and which codes for a polypeptide having the ability to bind TNF.

8. A recombinant DNA molecule, characterized in that it contains the DNA sequence defined in claim 1, or a degenerate variant or a fragment thereof.

5 9. A recombinant DNA molecule, which is replicable in prokaryotic or eukaryotic host organisms, wherein said DNA molecule contains expression control sequences functionally linked to the DNA sequence defined in claim 2, or a degenerate variant or a fragment thereof.

10 10. The recombinant DNA molecule according to claim 9, which is replicable in mammalian cells.

15 11. A recombinant DNA molecule designated pADTNF-BP.

12. A recombinant DNA molecule designated pADBTNF-BP.

20 13. A recombinant DNA molecule, replicable in prokaryotic or eukaryotic host organisms, characterized in that it codes for a TNF binding protein or functional derivative of the TNF binding protein, wherein said functional derivative binds TNF.

25 14. The recombinant DNA molecule according to claim 13, replicable in mammalian cells.

15. The recombinant DNA molecule according to claim 14 designated pADTNF-R.

30 16. The recombinant DNA molecule according to claim 14 designated pADBTNF-R.

17. A host cell transformed the recombinant DNA molecule of claim 8 or 9.

18. A host cell transformed with the recombinant DNA molecule of claim 13.

5 19. A substantially pure recombinant polypeptide coded by the DNA of claim 1.

10 20. The substantially pure polypeptide according to claim 19, characterized in that it is the TNF receptor of formula

15 met gly leu ser thr val pro asp leu leu leu pro leu val
leu leu glu leu leu val gly ile tyr pro ser gly val ile
gly leu val pro his leu gly asp arg glu lys arg asp ser
val cys pro gln gly lys tyr ile his pro gln asn asn ser
ile cys cys thr lys cys his lys gly thr tyr leu tyr asn
asp cys pro gly pro gly gln asp thr asp cys arg glu cys
glu ser gly ser phe thr ala ser glu asn his leu arg his
cys leu ser cys ser lys cys arg lys glu met gly gln val
glu ile ser ser cys thr val asp arg asp thr val cys gly
cys arg lys asn gln tyr arg his tyr trp ser glu asn leu
phe gln cys phe asn cys ser leu cys leu asn gly thr val
his leu ser cys gln glu lys gln asn thr val cys thr cys
his ala gly phe phe leu arg glu asn glu cys val ser cys
ser asn cys lys lys ser leu glu cys thr lys leu cys leu
pro gln ile glu asn val lys gly thr glu asp ser gly thr
thr val leu leu pro leu val ile phe phe gly leu cys leu
leu ser leu leu phe ile gly leu met tyr arg tyr gln arg
trp lys ser lys leu tyr ser ile val cys gly lys ser thr
pro glu lys glu gly glu leu glu gly thr thr lys pro
leu ala pro asn pro ser phe ser pro thr pro gly phe thr
pro thr leu gly phe ser pro val pro ser ser thr phe thr
ser ser ser thr tyr thr pro gly asp cys pro asn phe ala
ala pro arg arg glu val ala pro pro tyr gln gly ala asp
pro ile leu ala thr ala leu ala ser asp pro ile pro asn
pro leu gln lys trp glu asp ser ala his lys pro gln ser
leu asp thr asp asp pro ala thr leu tyr ala val val glu
asn val pro pro leu arg trp lys glu phe val arg arg leu
gly leu ser asp his glu ile asp arg leu glu leu gln asn
gly arg cys leu arg glu ala gln tyr ser met leu ala thr
trp arg arg arg thr pro arg arg glu ala thr leu glu leu
leu gly arg val leu arg asp met asp leu leu gly cys leu
glu asp ile glu glu ala leu cys gly pro ala ala leu pro
pro ala pro ser leu leu arg

45 or a fragment thereof which binds to TNF.

21. The substantially pure polypeptide according to claim 19, characterized in that it is TNF binding protein of the formula

5 asp ser val cys pro gln gly lys tyr ile his pro gln asn
asn ser ile cys cys thr lys cys his lys gly thr tyr leu
tyr asn asp cys pro gly pro gly gln asp thr asp cys arg
glu cys glu ser gly ser phe thr ala ser glu asn his leu
10 arg his cys leu ser cys ser lys cys arg lys glu met gly
gln val glu ile ser ser cys thr val asp arg asp thr val
cys gly cys arg lys asn gln tyr arg his tyr trp
ser glu asn leu phe gln cys phe asn cys ser leu cys leu
asn gly thr val his leu ser cys gln glu lys gln asn thr
15 val cys thr cys his ala gly phe phe leu arg glu asn glu
cys val ser cys ser asn cys lys lys ser leu glu cys thr
lys leu cys leu pro gln ile glu asn

or a functional derivative or fragment thereof having the ability to bind TNF.

20 *b* 22. A process for preparing a recombinant TNF ^{binding} _{receptor} protein, comprising cultivating the host cell of claim 17 and isolating the expressed recombinant TNF receptor protein.

25 *B* *B* *B* 23. A process for preparing a recombinant TNF ^{binding} _{receptor} protein, ~~or a functional derivative thereof which is capable of binding to TNF~~, comprising cultivating the host organism of claim 18 and isolating the expressed protein.

30 24. A pharmaceutical composition comprising a TNF receptor protein, or a functional derivative or fragment thereof, and a pharmaceutically acceptable carrier.

35 25. A method for ameliorating the harmful effects of TNF in an animal, comprising administering to an animal in need of such treatment a therapeutically effective amount of a TNF receptor polypeptide, or fragment thereof which binds to TNF.

26. A method for the detection of TNF in a biological sample, comprising contacting said sample with an effective amount of a TNF receptor polypeptide, or fragment thereof which binds to TNF, and detecting whether a complex is formed.



A handwritten signature in black ink, appearing to read "Alan C. H. Tso". The signature is written in a cursive style with a large, stylized "A" at the beginning. The "C" is enclosed in a triangular outline, and the "H" and "Tso" are written in a smaller, more fluid script.